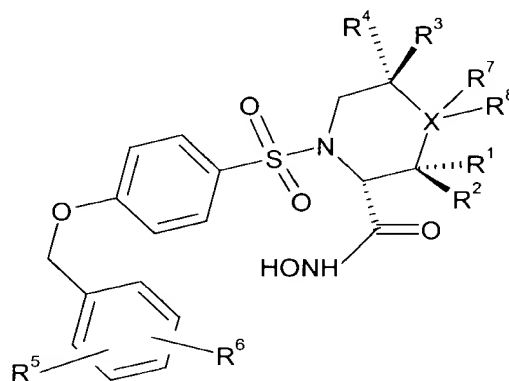


SELECTIVE INHIBITION OF AGGREGANASE IN OSTEOARTHRITIS TREATMENTAbstract

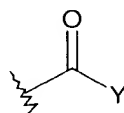
This invention relates to a method of treatment for osteoarthritis involving inhibitors of aggrecanase that demonstrate IC_{50} s of less than 20 nM and demonstrate differential potency against matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinases (ADAMs or reprolysins). This invention also relates to compounds, methods of treatment and composition of Formula I:



I

or a therapeutically acceptable salt thereof, wherein

- 10 X is carbon or nitrogen;
 R^1 and R^2 are independently selected from the group consisting of hydrogen, hydroxy, and methyl, wherein at least one of R^1 and R^2 is methyl;
 R^3 and R^4 are independently selected from the group consisting of hydrogen, hydroxy, and methyl, or R^3 and R^4 may be taken together to form a carbonyl group; and
 15 R^5 and R^6 are independent substituents in the ortho, meta, or para positions and are independently selected from the group consisting of hydrogen, halogen, cyano, methyl, and ethyl;
 with the provisos:
 when X is carbon, then R^7 and R^8 are both hydrogen and at least one of R^1 , R^2 , R^3 ,
 20 and R^4 is hydroxy;
 when X is carbon and R^5 is para-halo, then at least one of R^6 , R^3 , and R^4 is not hydrogen;
 when X is nitrogen, then R^8 is not present and R^7 is hydrogen or a group of the formula:



wherein, Y is $-\text{CH}_2-\text{NH}_2$ or $-\text{NH}-\text{CH}_3$; and

when X is nitrogen and R^7 is H, then R^3 and R^4 are taken together to form a carbonyl group.